UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/555,349	08/01/2000	THOMAS F. TEDDER	180/95/PCT/U	1602

7590 04/24/2002

ARLES A TAYLOR JR
JENKINS & WILSON
UNIVERSITY TOWER
3100 TOWER BOULEVARD SUITE 1400
DURHAM, NC 27707

EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	17

DATE MAILED: 04/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/555,349	Applicant(s) TEDDER, THOMAS F.
	Examiner Janice Li	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7 and 14-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *29 and 30* is/are allowed.

6)☒ Claim(s) *1-5,7 and 14-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The amendment filed on January 18, 2002 has been entered and assigned as Paper No. 15. Claims 6 and 8-13 have been canceled. Claims 1 and 2 have been amended. Claims 29 and 30 are newly submitted.

Claims 1-5, 7, 29, and 30 are pending and under current examination.

Rejections and objections that are not reiterated in this Office action are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION REQUIREMENT

The prior rejection of claims 1-13 is withdrawn in view of the amendment to the claims.

However, a new ground of rejection necessitated by the amendment appears below.

Claims 1-5, and 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

These claims are directed to a method for production of a monoclonal antibody to an antigen comprising immunizing an animal having B lymphocytes exhibiting a transmembrane signal transduction response of a degree not observed in conventional B lymphocytes ...". The specification does not define the above claim recitation, but discloses a CD19 mediated transmembrane signal transduction response in the mouse, wherebi the overexpression of CD19 would enhance the production of antibodies in the transgenic mice. With regard to the concept of transmembrane signal transduction, PubMed defines, "THE INTERCELLULAR OR INTRACELLULAR TRANSFER OF INFORMATION (BIOLOGICAL ACTIVATION/INHIBITION) THROUGH A SIGNAL PATHWAY. IN EACH SIGNAL TRANSDUCTION SYSTEM, AN ACTIVATION/INHIBITION SIGNAL FROM A BIOLOGICALLY ACTIVE MOLECULE (HORMONE, NEUROTRANSMITTER) IS MEDIATED VIA THE COUPLING OF A RECEPTOR/ENZYME TO A SECOND MESSENGER SYSTEM OR TO AN ION CHANNEL. SIGNAL TRANSDUCTION PLAYS AN IMPORTANT ROLE IN ACTIVATING CELLULAR FUNCTIONS, CELL DIFFERENTIATION, AND CELL PROLIFERATION. EXAMPLES OF

SIGNAL TRANSDUCTION SYSTEMS ARE THE GAMMA-AMINOBUTYRIC ACID-POSTSYNAPTIC RECEPTOR-CALCIUM ION CHANNEL SYSTEM, THE RECEPTOR-MEDIATED T-CELL ACTIVATION PATHWAY, AND THE RECEPTOR-MEDIATED ACTIVATION OF PHOSPHOLIPASES. THOSE COUPLED TO MEMBRANE DEPOLARIZATION OR INTRACELLULAR RELEASE OF CALCIUM INCLUDE THE RECEPTOR-MEDIATED ACTIVATION OF CYTOTOXIC FUNCTIONS IN GRANULOCYTES AND THE SYNAPTIC POTENTIATION OF PROTEIN KINASE ACTIVATION. SOME SIGNAL TRANSDUCTION PATHWAYS MAY BE PART OF LARGER SIGNAL TRANSDUCTION PATHWAYS; FOR EXAMPLE, PROTEIN KINASE ACTIVATION IS PART OF THE PLATELET ACTIVATION SIGNAL PATHWAY". The term "a transmembrane signal transduction response" is obvious generic to a considerable number of pathways, varying in the chemical structures and physiological functions; thus, B lymphocytes exhibiting an unconventional degree of a transmembrane signal transduction response would encompass numerous B cells having such generic characteristics. The specification fails to provide an adequate description to teach how many transmembrane signal transduction pathway are present in B lymphocytes, which of them are involved in antibody production and which of them are associated with disrupted peripheral tolerance. An adequate written description for the recited B lymphocytes requires more than a mere statement that it is part of the invention; what is required is a description of a distinct structure and associated physiological function of the B cell itself, e.g. a B lymphocytes that overexpress CD19. It is not sufficient to define the B lymphocyte solely by its principal biological property, i.e. "exhibiting a transmembrane signal transduction response of a degree not observed in conventional B lymphocytes", because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of a cell with that biological property. Also, naming a type of material generically known to exist,

in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all B lymphocytes that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific chemical and physical properties of a chemical, or the sequences of a protein and nucleic acids, the distinct structure of a cell, which provide the means for practicing the invention. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

The specification discloses a B lymphocyte with an unconventional CD19 transmembrane signal transduction response, however, it fails to teach the common attributes and structure-functional relationship for the genus of B lymphocytes having the recited characteristics. Further, the claims encompass animals selected from the group of a mouse, rat, pig, guinea pig, poultry, goat, sheep, primate and rabbit, however, the specification fails to teach the characteristics of B lymphocytes in different subgenera of animals, particularly with regard to the transmembrane signal transduction pathways. Thus, the specification fails to provide an enabling disclosure commensurate

with the scope of the claims. The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad classes of *B lymphocytes exhibiting a transmembrane signal transduction response of a degree not observed in conventiaonal B lymphocytes* and having a disrupted peripheral tolerance. Therefore, only the described B lymphocytes from CD19 transgenic mouse meets the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-5, and 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

These claims are drawn to using *B lymphocytes exhibiting an unconventional transmembrane signal transduction response* for enhanced production of antibodies. However, as indicated *supra* in the written description section, the specification fails to provide an adequate description for the numerous B lymphocytes encompassed by the claims. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed genus, transgenic CD19 alone is insufficient to describe the genus. One cannot extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structures of the B lymphocytes possess the recited characteristics, thus except the mouse CD19, one would not know how to use the invention without first carrying out undue

experimentation to determine which of the B lymphocytes would have the recited function.

In the response to the Office action Paper #11, applicants cite *In re Marzocchi* to argue that no specific scientific or other factual basis have been presented for rejections under 35 U.S.C 112, 1st paragraph, thus the Patent Office has not met its burden. It is noted that *Marzocchi* also teaches "IN THE FIELD OF CHEMISTRY GENERALLY, THERE MAY BE TIMES **WHEN WELL-KNOWN UNPREDICTABILITY OF CHEMICAL REACTIONS WILL ALONE BE ENOUGH TO CREATE REASONABLE DOUBT** AS TO ACCURACY TO **BROAD STATEMENT** PUT FORWARD AS ENABLING SUPPORT FOR CLAIM; THIS WILL ESPECIALLY BE THE CASE WHERE STATEMENT IS, ON ITS FACE, CONTRARY TO GENERALLY ACCEPTED SCIENTIFIC PRINCIPLES, ETC" *(In re Marzocchi and Horton, 169 USPQ 367 CCPA1971)*. For example, the instant claims read on a method for production of antibodies in a transgenic animal having B lymphocytes overexpressing CD19, wherein the animal is selected from broad subgenera, a doubt is reasonable since the art of transgene animal is still under development and highly unpredictable.

The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03), this is particularly true in the art of transgenic animals with respect to transgene behavior. Without evidence to the contrary, transgene expression in different species of transgenic animals is not consistent and varies according to the particular host species. This observation is supported by *Hammer et al. Hammer et al* report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The observation is further supported by *Mullins et al.* who report on transgenesis in the rat

and larger mammals. *Mullins et al.*(J Clin Invest 1996 Apr;97:1557-60) state that "THE MAJOR PROBLEM REGARDING PRONUCLEAR MICROINJECTION IS THAT THE EXOGENOUS DNA INTEGRATES RANDOMLY INTO CHROMOSOMAL DNA. POSITION EFFECTS, WHERE THE TRANSGENE IS INFLUENCED BY ITS SIT OF INTEGRATION IN THE HOST CHROMOSOME, CAN HAVE MAJOR CONSEQUENCES ON THE EXPRESSION OF THE TRANSGENE, INCLUDING LOSS OF CELL SPECIFICITY, INAPPROPRIATE HIGH COPY NUMBER-INDEPENDENT EXPRESSION AND COMPLETE SILENCING OF THE TRANSGENE" (paragraph bridging pages 1557-58), "A GIVEN CONSTRUCT MAY REACT VERY DIFFERENTLY FROM ONE SPECIES TO ANOTHER" (page 1559, Summary). Since the applicants only disclosed the example in a transgenic mouse, there is no way to predict whether a given phenotype having an unconventional B cell and an enhanced antibody production would generated in any other animals. *Wall et al.* further report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies" (page 2215, first paragraph). Thus, it is incumbent upon applicants to provide sufficient teaching to enable the claimed invention.

Therefore, in view of the limited guidance, the lack of predictability of the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejection of claims 1-4, 6-10, 12, 13 under 35 U.S.C. 102(b) as being anticipated by *Hammerling et al* is withdrawn in view of the amendment.

The prior rejections of claims 1, 3, 4, 6, 7 under 35 U.S.C. 102(b) as being anticipated by *WO9614401* is withdrawn in view of the amendment.

Conclusion

Claims 29 and 30 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
April 12, 2002

JAMES KETTER
PRIMARY EXAMINER